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Evaluating a novel formula for noninvasive estimation of arterial
carbon dioxide during postresuscitation care

Short title: Formula for estimating arterial CO₂

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Conflicts of interest

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from Covidien and BARD Medical (Ireland). Authors Erkki Heinonen and Tom Häggblom are
employees of GE Healthcare.

Abstract

Background

Controlling arterial carbon dioxide is paramount in mechanically ventilated patients, and an accurate and continuous noninvasive monitoring method would optimize management in dynamic situations. In this study, we validated and further refined formulas for estimating partial pressure of carbon dioxide with respiratory gas and pulse oximetry data in mechanically ventilated cardiac arrest patients.

Methods

A total of 4,741 data sets were collected retrospectively from 233 resuscitated patients undergoing therapeutic hypothermia. The original formula used to analyze the data is $\text{PaCO}_2\text{-est1} = \text{PETCO}_2 + k[(\text{PIO}_2 - \text{PETCO}_2) - \text{PaO}_2]$. To achieve better accuracy, we further modified the formula to $\text{PaCO}_2\text{-est2} = k_1 * \text{PETCO}_2 + k_2 * (\text{PIO}_2 - \text{PETCO}_2) + k_3 * (100 - \text{SpO}_2)$. The coefficients were determined by identifying the minimal difference between the measured and calculated arterial carbon dioxide values in a development set. The accuracy of these two methods was compared with the estimation of the partial pressure of carbon dioxide using end-tidal carbon dioxide.

Results

With $\text{PaCO}_2\text{-est1}$, the mean difference between the partial pressure of carbon dioxide, and the estimated carbon dioxide was 0.08 kPa (SE $\pm$ 0.003); with $\text{PaCO}_2\text{-est2}$ the difference was 0.036 kPa (SE $\pm$ 0.009). The mean difference between the partial pressure of carbon dioxide and end-tidal carbon dioxide was 0.72 kPa (SE $\pm$ 0.01). In a mixed linear model, there was a significant difference between the estimation using end-tidal carbon dioxide and $\text{PaCO}_2\text{-est1}$ ($p < 0.001$) and $\text{PaCO}_2\text{-est2}$ ($p < 0.001$), respectively.

Conclusions

This novel formula appears to provide an accurate, continuous, and noninvasive estimation of arterial carbon dioxide.

Introduction

Monitoring carbon dioxide is paramount in mechanically ventilated patients and commonly performed by measuring the partial pressure of carbon dioxide (PaCO_2) with arterial blood gas (ABG) analysis. Although an ABG analysis intermittently provides exact PaCO_2 values, PaCO_2 may change despite constant ventilation.

End-tidal carbon dioxide generally underestimates arterial PaCO_2 .¹ End-tidal carbon dioxide is affected by the ventilation/perfusion ratio (V/Q ratio), possible cardiac disease such as right-to-left shunt, and increased dead space.² Maintaining normoventilation may be difficult under circumstances where ABG measurements is not available, including prehospital care and patient transport.³ The measurement of PETCO_2 with continuous capnography is used as a surrogate but may be a poor indicator of PaCO_2 because of V/Q mismatch. Dyscarbia and unintentional deviation from normoventilation have been associated with poor outcome.⁴⁻⁵ Therefore, seeking new dynamic methods to noninvasively estimate PaCO_2 is highly important.⁶

We present a method for estimating the PaCO_2 level in a continuous and noninvasive way. Previously, we tested a formula for estimating arterial carbon dioxide partial pressures in an experimental model and found good agreement between this formula with measured PaCO_2 values in various physiological and pathophysiological conditions.⁷ The formula was developed based on the assumption that the degree of V/Q mismatch behind the alveolar–arterial oxygen tension difference (PA-aO_2) is similar for both O_2 and CO_2 . In our previous study, the estimation of PaO_2 was evaluated purely under experimental conditions. The primary aim of the present study was to test the agreement of measured PaCO_2 and estimated PaCO_2 by the original formula in mechanically ventilated cardiac arrest (CA)

patients. The secondary aim was to validate and refine this formula to achieve a better agreement. In addition, we studied whether the accuracy of the current formulas was affected by patient temperatures and the mean arterial blood pressure levels.

Methods

Study subjects and settings

We conducted a retrospective study in mechanically ventilated adult (≥ 18 years of age) patients who were treated after CA in a tertiary academic hospital between October 2012 and September 2016. Research approval was obtained from the Hospital District of Helsinki and Uusimaa (HUS/420/2018 25.04.2018).

Collected data

From the hospital laboratory records, we collected the data of temperature-corrected PaCO₂ samples taken within the first 48 hours of ICU admission. Physiological data, including respiratory gas values, peripheral oxygen saturation (SpO₂), and body temperature at the time points corresponding to each ABG sampling, were collected from the ICU electronic patient data management system (Picis, Wakefield, MA, USA). Patient characteristics, such as age, height, weight, and gender, were collected from the ICU electronic patient data management system. Comorbidities and resuscitation factors were collected from electronic patient medical records (Uranus, CGI, Canada). Organ dysfunction and severity of illness scores (Sequential Organ Failure Assessment [SOFA]; the Simplified Acute Physiology Score II [SAPS II]); and the Acute Physiology and Chronic Health Evaluation II [APACHE II]) scores were retrieved from the Finnish Intensive Care Quality Consortium Database (Tieto Healthcare & Welfare Oy, Espoo, Finland).⁸⁻¹⁰

Estimation of arterial CO₂ partial pressure

The original formula used for estimating PaCO₂ has been published previously and is defined as follows: ⁷

$$\text{PaCO}_2\text{-est1} = \text{PETCO}_2 + k[(\text{PIO}_2 - \text{PETCO}_2) - \text{PaO}_2]$$

where PETCO₂ is the measured end-tidal CO₂ pressure and PIO₂ is the measured inspired O₂ pressure with the equation of FIO₂ x (barometric pressure – saturated vapor pressure of H₂O). PaO₂ is estimated from the oxygen dissociation curve. ¹¹ This formula was developed further in an attempt to improve accuracy. The patient population was divided randomly into derivation and validation groups. Using linear regression, we used derivation data to compose the new, calibrated formula and to determine the calibration factors that would minimize the difference between estimated and measured PaCO₂ values.

Creation of the calibrated, new formula (PaCO₂-est2)

The relationship factors were defined by fitting the data points for the minimal difference between the blood gas measured PaCO₂ and the novel formula estimated value. For this purpose, 6,580 data points measured from the 233 patients were divided into two groups according to PETCO₂ values. Data points having PETCO₂ < 3 kPa were excluded as potentially artifactual, for example, a leak caused by side-stream gas sampling. The remaining data were randomly allocated to a derivation group of 50 patients. The remaining 183 patients composed the validation group. The 1008 data sets of the derivation group were divided according to a PETCO₂ value of 4 kPa. The 4 kPa division value was randomly selected to reflect potentially major (< 4 kPa) and normal or minor (≥ 4 kPa) V/Q mismatches that could result in different relationship factors. We defined different validation coefficients, called k-factors, for data sets depending on the measured carbon dioxide level, keeping the 4 kPa

threshold. The potentially major V/Q mismatch group included 255 data sets, and the potentially normal or minor mismatch group included 753 data sets. The remaining data sets—3,504 in total—composed the validation group. The study flowchart is presented in Supplementary Figure 1.

Using the least square fitting to minimize the difference between the estimated PaCO₂ and ABG PaCO₂ values, the equation coefficients were determined for both the major and the normal or minor V/Q mismatch groups separately. These coefficients were then used to calculate the estimated PaCO₂ for the validation group data points comprising the presented validation result statistics. The values for the coefficients are presented in Table 1.

After adjustments, the formula (PaCO₂-est2) is defined as follows:

$$\text{PaCO}_2\text{-est2} = k_1 * \text{PETCO}_2 + k_2 * (\text{PIO}_2 - \text{PETCO}_2) + k_3 * (100 - \text{SpO}_2)$$

PaCO₂ is the arterial CO₂ partial pressure, and PETCO₂ and PIO₂ are the end-tidal CO₂ and inspired O₂ pressures, respectively, recorded with a side-stream gas analyzer (GE Healthcare, Milwaukee, Wisconsin, USA). SpO₂ is the peripheral hemoglobin oxygen saturation measured with a pulse oximeter.

The O₂ difference in this hypothesis is based on the estimation of PETO₂-PaO₂ with the aid of standard bedside monitored parameters. It is well-known that the O₂ difference (PIO₂-PETO₂) is approximately PETCO₂, providing an estimate for PETO₂ (PIO₂-PETCO₂).¹²

Conceptually, this equation is based on the hypothesis that the physiological factors causing the alveolar–arterial tension difference are similar for both O₂ and CO₂:

ventilation/perfusion mismatch in the form of left-to-right shunt perfusion and alveolar dead-space ventilation. The equation aims to detect the magnitude of these gas exchange disorders.

181 In shunt perfusion part of the pulmonary artery blood flow is passing the lungs without
182 communicating with the alveoli. In pulmonary vein this shunted blood of venous O₂ content
183 mix with the blood flow representing alveolar gas composition. Affinity of low oxygen
184 saturation of the shunted perfusion reduces the mixture oxygen partial pressure from the
185 alveolar equilibrium. Depending on the shunt, the magnitude of dissolved O₂ may be
186 insufficient to fully saturate the Hb, which is measured as SpO₂ below 100%. The difference
187 (100-SpO₂) measures the magnitude of this insufficiency. Clinician may respond to reduced
188 SpO₂ by increasing the PIO₂. This compensatory action increases the second term of the
189 equation.

190 In alveolar dead space no gas exchange occurs with the alveolar blood flow, which
191 reduces SpO₂. Thus, increase on the term (100-SpO₂) of the equation indicates the increase
192 in alveolar dead space. Again, clinician may respond to reduced SpO₂ by increasing the PIO₂
193 increasing respectively the second term of the equation. The gas in alveolar dead space
194 remains in inspired concentrations and dilutes at upper respiratory tract reducing PETCO₂.
195 This increases the second term as indication of the alveolar dead space. In addition to a V/Q
196 mismatch, possible differences in CO₂ and O₂ alveolar exchange may cause additional
197 differences between PETCO₂ and PaCO₂ not reflected in the O₂ difference; for example
198 diffusion disturbance. Each factor was assigned a relationship coefficient, the values of
199 which were determined by the calibration data points.

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201 **Measuring the change in the accuracy of estimation of PaCO₂ over time**

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We divided the 48-hour study period into three-hour intervals; in cases with more than one sample per three-hour period, we calculated the mean of the differences between the measured and estimated PaCO₂ values.

Statistical analyses

To validate PaCO₂-est1 and the comparisons used between PaCO₂-est2 and PETCO₂, we calculated the mean difference with the standard deviation (SD) between the measured and estimated PaCO₂ values. We assessed the agreement between the measured and estimated PaCO₂ values using the Bland-Altman analysis. We used the software created by Olofsen et al. for the Bland-Altman analysis, including the bias with +/-SE and the limits of agreement with 95% confidence intervals.¹³ Percentage error was calculated from the SD of agreement and mean CO₂: $100 * (1,96 * SD / \text{mean CO}_2)$.

Other analyses were performed using Statistical Package for Social Sciences (SPSS), version 25 (IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY, IBM Corp.). Within-subject (WSV) and between-subject variances (BSV), intraclass correlations (τ), and repeatability coefficients were estimated for the differences between estimated PaCO₂ and ETICO₂. The Bland-Altman method used controls for the effect of repeated measures by calculating the within-subject and between-subject variations. The normality of the distribution of the differences between the measured and estimated values was tested using the Kolmogorov–Smirnov test.

A comparison of the differences between estimations provided by PaCO₂-est2 and PETCO₂ was performed using a mixed linear model in which time and measured values were treated as fixed effects, whereas subjects and formulas were treated as random effects.

226 Also, using a mixed linear model, we tested the accuracy of the formulas over time and
227 whether there was any interaction between the performance of the formulas and the mean
228 arterial blood pressure or patient temperature. We also examined the accuracy of the
229 methods in different PaCO₂ and O₂ levels by dividing the data in deciles, according to the
230 measured PaCO₂ and FIO₂ level.

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Results

In total, we included 233 patients and collected 4,741 datasets. The basic patient characteristics are shown in Table 2. We excluded two patients because of missing data for the inspired gas O₂ concentrations. The mean number of ABG samples per patient was 15 (SD 10). One of the CAs was in the hospital and the other 232 were out of the hospital. All patients were treated with therapeutic hypothermia. Table 3 shows the baseline information about the ventilator parameters and hemodynamics during the 48-hour study period.

Difference between the estimated and measured PaCO₂ values (PaCO₂-est1)

The mean difference between the measured and estimated PaCO₂ values ($\text{PaCO}_2 = \text{PETCO}_2 + k[\text{PIO}_2 - \text{PETCO}_2] - \text{PaO}_2$) was 0.08kPa (SE $\pm$ 0.003). The SD of the differences was 0.62 (SE $\pm$ 0.015), percentage error was 24%. The Bland-Altman plot demonstrating the agreement between the PaCO₂-est1 and measured PaCO₂ values with limits of agreement and their 95% confidence intervals is presented in Figure 1.

Intraclass correlation (PaCO₂-est1)

The within-subject variance for the estimated PaCO₂ (PaCO₂-est1) and measured PaCO₂ values was 0.20 (SE $\pm$ 0.004). The between-subjects variance was 0.19 (SE $\pm$ 0.018). The intraclass correlations (τ = ratio of BSV and total variance) for the estimated PaCO₂ and measured PaCO₂ values were τ 0.48 (SE $\pm$ 0.025, Spearman's ρ -0.105, SE $\pm$ 0.029).

Difference between the estimated and measured PaCO₂ values (PaCO₂-est2)

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267 The data for the PaCO₂ values were not normally distributed (Kolmogorov–Smirnov test, p
268 value < 0.001). The mean difference between the measured and PaCO₂-est2 values was
269 0.036 kPa (SE ± 0.009). The SD of the differences was 0.59 (SE ± 0.06), percentage error was
270 23%. The mean difference between the measured PaCO₂ and ETCO₂ values was 0.71 kPa (SE
271 ± 0.010), percentage error was 24%. The SD of the differences was 0.62 (SE ± 0.07). There
272 was a statistically significant difference between PaCO₂-est2 and end-tidal CO₂ in estimating
273 PaCO₂ (p < 0.001). Also, there was a statistically significant difference (p < 0.001) when
274 comparing the true and estimated values with the original, unmodified formula (PaCO₂-
275 est1) and modified formula (PaCO₂-est2).

276 The Bland-Altman plots demonstrating the agreement between the PaCO₂-est2 and
277 measured PaCO₂ values, as well as the PaCO₂ (PETCO₂) and measured PaCO₂ values with
278 limits of agreement and their 95% confidence intervals, are presented in Figure 2a and 2b,
279 respectively. The accuracy of the PaCO₂-est2 was not affected by the patients' temperature
280 (Supplementary Figure 1). There was no statistically significant difference between the
281 methods at different mean arterial pressure levels (Supplementary Figure 2). PaCO₂-est2
282 was superior to PaCO₂-est1a nd end-tidal CO₂ at different temperature and blood pressure
283 levels.

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285 **The effect of time**

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287 The mean difference between the measured PaCO₂ values and estimated PaCO₂ values in
288 the first three hours was 0.12kPa (SE +/- 0.041) when using PaCO₂-est2. The SD of the
289 differences was 0.73. The mean difference between the measured and estimated PCO₂

values changed over time according to the linear mixed model analysis. These changes, however, were not significant ($p=0.06$). The mean differences between the measured and estimated PaCO_2 levels by both methods— PETCO_2 and $\text{PaCO}_2\text{-est2}$ —on three-hour intervals starting from the first ABG sample are presented in Figure 3.

The effect of different carbon dioxide and inspired oxygen levels on the accuracy of $\text{PaCO}_2\text{-est2}$

Estimations carried out with $\text{PaCO}_2\text{-est2}$ were the most accurate in normoventilation. The differences between the measured and estimated PaCO_2 in PaCO_2 deciles are shown in Figure 4a. The difference between the measured and estimated PaCO_2 values was not affected by FIO_2 values at the same degree as PaCO_2 levels. The differences between the measured and estimated PaCO_2 values in FIO_2 deciles are shown in Figure 4b.

The intraclass correlation

The WSV for the estimated PaCO_2 and ETCO_2 values were 0.16 ($\text{SE} \pm 0.004$) and 0.18 ($\text{SE} \pm 0.004$), respectively. The intraclass correlations (τ = ratio of BSV and total variance) for the estimated PaCO_2 and PETCO_2 values were τ 0.48 ($\text{SE} \pm 0.028$, Spearman's ρ 0.16 , $\text{SE} \pm 0.033$) and ETCO_2 0.61 ($\text{SE} \pm 0.027$, Spearman's ρ -0.05 , $\text{SE} \pm 0.034$).

Discussion

We developed and validated a novel formula that utilizes respiratory gas measurements and SpO_2 for estimating PaCO_2 noninvasively in mechanically ventilated patients. We found a good agreement between measured and estimated PaCO_2 values for the novel formula and found no evidence of impaired accuracy depending on patient temperature and mean arterial pressure levels. This formula might enable reliable, noninvasive methods for monitoring mechanical ventilation. The difference between the measured and estimated PaCO_2 values in our study is below the limit of agreement of a clinically acceptable 1 kPa error.¹⁴

In healthy subjects, there is a reasonable agreement between PETCO_2 and arterial PaCO_2 , especially with temperature corrected PaCO_2 .¹⁵⁻¹⁶ By contrast, with respiratory or cardiac failure, the gap between PaCO_2 and ETCO_2 widens because of V/Q mismatch, which results in lower alveolar and expired breathing gas CO_2 levels. In some studies, there has been a strong agreement between PETCO_2 and PaCO_2 .¹⁷⁻¹⁹ Other studies have reported that the gradient between PETCO_2 and PaCO_2 has clinically significant importance considering for example the reliability of monitoring and the adequacy of ventilation.²⁰⁻²¹ In patients with hypotension and metabolic acidosis, the gap between PETCO_2 and PaCO_2 is higher than in normotensive and stable patients.²²

The accuracy of the novel formula is the highest in the normoventilation range. Previous studies of end-tidal CO_2 and PtcCO_2 and show similar results with high PaCO_2 levels,

which can be the result of increased dead space and shunting.²²⁻²³ The method underestimated the highest PaCO_2 values, which may occur with large alveolar dead space. The PACO_2 of perfused alveoli equilibrates with blood concentration to maximum venous CO_2 concentration independently of the alveolar dead space whereas in the alveolar dead space the concentration remains zero of the inspired gas. At expiration the zero concentration dead space gas dilutes the blood concentration stream from perfused alveoli causing the PETCO_2 reduction corresponding to the amount of dead space ventilation. The alveolar dead space effect on oxygen is minor: the PAO_2 of the perfused alveoli will decrease more in supplying the whole perfusion with smaller gas volume. During expiration, when mixing in the upper airways, the inspired oxygen concentration from the dead space compensates the reduced PAO_2 from the perfused lung regions. As a result of this compensation in oxygenation, the equation is unable to fully compensate the alveolar dead space effect on the PaCO_2 .

Patient temperatures did not affect the formula's accuracy. This is important because patients in prehospital care are more likely to suffer from hypothermia²⁴ and targeted temperature management is standard practice during the intensive care of patients after CA.

The mean difference between the measured and estimated values was slightly higher in the first three hours compared with the remaining 45 hours but this difference was not statistically significant. In previous studies, the difference between PETCO_2 and PaCO_2 has been reported to increase over time.²⁵

There was a statistically significant difference between the PaCO_2 estimates obtained using the two formulas ($\text{PaCO}_2\text{-est1}$ and $\text{PaCO}_2\text{-est2}$). An improvement regarding $\text{PaCO}_2\text{-est2}$ compared with $\text{PaCO}_2\text{-est1}$ is that $\text{PaCO}_2\text{-est2}$ utilizes data directly from the

pulse oximeter instead of PaO_2 estimated by SpO_2 obtained from the oxygen dissociation curve.

In emergency care despite its unreliability for determining the adequacy of ventilation²⁶, PETCO_2 is a useful tool in verifying the correct positioning of an endotracheal tube.²⁷ Transcutaneous CO_2 is routinely used in neonatal ICUs.²⁸ In adults, PtcCO_2 has shown conflicting results²⁹⁻³⁰ and may be affected by hypotension, peripheral perfusion disturbances and the use of vasoconstrictors.³¹⁻³² Transcutaneous PCO_2 appears to be a more accurate method compared with PETCO_2 , but its accuracy might deteriorate with extreme PaCO_2 values and is also affected by V/Q mismatch.^{33-34, 23}.

There are some limitations to this study. One patient was hemodynamically unstable and potentially had a very low cardiac output (CO). In conditions associated with low CO, PETCO_2 does not correlate with PaCO_2 values, but unfortunately, the CO value was not available for assessment in this case.³⁵ Our next aim is to identify the limitations of the algorithm and validate the formula in different critically ill mechanically ventilated patient groups.

In conclusion the present study shows that a novel formula developed for estimating PaCO_2 values has good agreement with measured ABG values and outperforms PETCO_2 in accuracy. Within certain limits, it offers a noninvasive and continuous method for assessing PaCO_2 .

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Table 1. Coefficients k_1 , k_2 , and k_3 for Formula 2 as determined by using 500 randomly selected data points. The coefficients were created separately for the low and high PETCO₂ groups.

	k_1	k_2	k_3
PETCO ₂ -low (<4 kPa)	1.178	0.0132	0.0185
PETCO ₂ -high ($\geq$ 4 kPa)	1.049	0.0162	0.0139

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Table 2. Characterization of patients and various subgroups of interest

<i>Patient characteristics</i>	
Age, years	62 (52-67)
Male sex, n (%)	181 (81)
Height, cm	179 (172-183)
Weight, kg	85 (75-90)
<i>Initial rhythm, n (%)</i>	
VF	228 (97.9)
VT	2 (0.85)
PEA	2 (0.85)
Asystole	1 (0.4)
ROSC, min	20 (15-25)
<i>Scoring model, n (IQR)</i>	
APACHE II	25 (18-31)
SAPS	47 (35-64)
SOFA	8 (7-10)
<i>Prevalence of lung disease, no (%)</i>	
Asthma	18 (7.7)
COPD	11 (4.7)
Interstitial lung disease	2 (0.85)

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523 **Table 3.** Characteristics of ventilation and hemodynamic variables during first and second
524 intensive care unit (ICU) treatment days. Data are shown as median (interquartile range).

	Day 1	Day 2
FIO ₂ , %	35 (30-49)	35 (30-45)
SpO ₂ ,%	99 (98-100)	99 (97-99)
PEEP, cmH ₂ O	7 (6-8)	7 (6-8)
HR	55 (45-68)	66 (55-79)
MAP, mmHg	78 (73-86)	77 (72-84)
PETCO ₂ , kPa	4.2 (3.8-4.7)	4.6 (4.1-5.1)
PaCO ₂ , kPa	5.0 (4.5-5.4)	5.2 (4.9-5.6)
PaO ₂ /FIO ₂ -ratio	210 (36-303)	198 (36-310)

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Figure 1. The Bland-Altman plot assessing agreement between PaCO₂ (PaCO₂-est1) and measured PaCO₂

534 **Figure 2a.** The Bland-Altman plot assessing agreement between PaCO₂ (PaCO₂-est2) and
535 measured PaCO₂

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538 **Figure 2b.** The Bland-Altman plot assessing agreement between ETCO_2 and measured PaCO_2

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Figure 3. The mean differences between measured PaCO₂ and estimated PaCO₂, and mean differences between measured PaCO₂ (Formula 2) and end-tidal CO₂ at different time periods

546 **Figure 4a.** The mean differences between measured PaCO₂ and estimated PaCO₂ (Formula
 547 2) , and mean differences between measured PaCO₂ and end-tidal CO₂ at CO₂ deciles

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550 **Figure 4b.** The mean differences between measured PaCO_2 and estimated PaCO_2 (Formula
 551 2) , and mean differences between measured PaCO_2 and end-tidal CO_2 at FiO_2 deciles

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1. **Supplementary Figure 1.** Flowchart of the study population

1. **Supplementary Figure 2.** The difference between measured and estimated PaCO₂ at different body temperatures.

2. **Supplementary Figure 3.** The mean differences between measured and estimated PaCO₂ (Formula 1, Formula 2, and end-tidal CO₂) at different mean arterial pressure levels.

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570 **Table 2** .Patients' characteristics and pre-hospital variables. All continuous values are given
571 as medians (interquartile range), and categorical values as percentages. Cm=centimeters,
572 kg=kilograms, VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless
573 electrical activity, ROSC=Return of spontaneous circulation, COPD= chronic obstructive
574 pulmonary disease

575 **Table 3**. Hemodynamic variables and variables of ventilator settings and derived data. All
576 continuous values are given as medians (interquartile range). FIO₂=fraction of inspired
577 oxygen, SpO₂=partial oxygen saturation of the arterial blood, PEEP=positive end-expiratory
578 pressure, HR=heart rate, MAP=mean arterial pressure; etCO₂=end-tidal carbon dioxide;
579 PaCO₂=arterial partial pressure of carbon dioxide; PaO₂/FIO₂= arterial oxygen partial
580 pressure/fractional inspired oxygen ratio

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583 **Figure 1**. Bland-Altman plots with 95% limits of agreement with 95% confidence intervals
584 demonstrating agreement between partial pressure of carbon dioxide, PaCO₂ (Formula 1),
585 and measured PaCO₂ during the first 48 hours after admission to the ICU.

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587 **Figures 2a and 2b**. Bland-Altman plots with 95% limits of agreement with 95% confidence
588 intervals demonstrating agreement between the PaCO₂ (Formula 2) and measured PaCO₂
589 values (a) and the ETCO₂ and measured PaCO₂ values (b) during the first 48 hours after
590 admission to the ICU.

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Figure 3. Mean differences between the measured and estimated PaCO₂ values and between measured PaCO₂ and end-tidal CO₂ at different time points: First time period: 0–3 hours; 2nd: 3–6 hrs; 3rd 6–9 hrs; 4th 9–12 hrs; 5th 12–15 hrs; 6th 15–18 hrs; 7th 18–21 hrs; 8th: 21–24 hrs; 9th: 24–27 hrs; 10th 27–30 hrs; 11th 30–33 hrs; 12th: 33–36 hrs; 13th: 36–39 hrs; 14th: 39–42 hrs; 15th: 42–45 hrs; and 16th: 45–48 hrs.

Figures 4a and 4 b. The mean differences between measured PaCO₂, estimated PaCO₂ (Formula 2) and end-tidal CO₂ values at different levels of PaCO₂. 1: PaCO₂ < 4.3 kPa; 2: PaCO₂ 4.3-4.5 kPa; 3: PaCO₂ 4.6-4.7 kPa; 4: PaCO₂ 4.8-4.9 kPa; 5: PaCO₂ 5.0-5.1 kPa; 6: PaCO₂ 5.2 kPa; 7: PaCO₂ 5.3-5.4 kPa; 8: PaCO₂ 5.5-5.6 kPa; 9: PaCO₂ 5.7-5.9 kPa; and 10: PaCO₂ > 5.9 kPa. The mean differences between the measured PaCO₂, estimated PaCO₂ (Formula 2), and end-tidal CO₂ values at different levels of FIO₂ (%). 1: FIO₂ < 26; 2: FIO₂ 26–30; 3: FIO₂ 30–30.3; 4: FIO₂ 30.3–34.6; 5: FIO₂ 34.6–35.2; 6: FIO₂ 35.2–40.0; 7: FIO₂ 40.0–45.0; 8: FIO₂ 45.0–50.33; 9: FIO₂ 50.33–60.55; and 10 FIO₂ > 60.55.

Supplementary Figure 1. Flowchart of the study population. V/Q mismatch=ventilation/perfusion mismatch; ETCO₂=end-tidal carbon dioxide; kPa=kilopascal

Supplementary Figure 2. The difference between the measured and estimated PaCO₂ values at different body temperatures. PaCO₂=Partial pressure of arterial carbon dioxide; ETCO₂=end-tidal carbon dioxide.

615 **Supplementary Figure 3.** The mean differences between the measured and estimated
616 PaCO₂ values (Formula 1, Formula 2, and end-tidal CO₂) at different mean arterial pressure
617 levels. PaCO₂=Partial pressure of arterial carbon dioxide; ETCO₂=end-tidal carbon dioxide.
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